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14. ABSTRACT

Severe bone loss commonly occurs in individuals with chronic spinal cord injury who are non weight-bearing and leads to an increased risk of lower extremity fractures. This 12 month multi-side, double-blind, randomized, placebo-controlled study evaluates the efficacy and safety of two interventions known to be anabolic to bone, parathyroid horomone and mechanical loading (provided as teriparatide and vibration respectively). In 60 SCI individuals with low bone mass. At the end of the third year of this project, enrollment has been completed there are 24 participants (40%) who have completed year 1 of the study; 55% of participants are still active during the first year of the study and 5% have elected not to continue. No safety issues have arisen during the course of the study. Results regarding efficacy will only be available at the completion of the trial.

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INTRODUCTION:

After acute spinal cord injury (SCI), individuals unable to ambulate experience rapid and profound bone loss of as much as 50% in their lower extremities over the ensuing 2-5 years. This bone loss results in their having a significantly increased risk of fracture thereafter. This study evaluates the ability of two interventions, parathyroid hormone and mechanical loading, separately and together, to increase bone mass and improve bone quality in individuals with chronic SCI and low bone mass. These interventions have previously been shown to be effective in increasing bone mass and decreasing fractures in non-disabled populations of men and post-menopausal women but not examined in individuals with SCI. In this three-arm, modified factorial design, double-blind, placebo-controlled study, 60 people with chronic SCI will receive daily teriparatide and mechanical vibration. Assessment of bone mass (by DXA scanning and quantitative computed tomography), bone quality (by finite element modeling), and bone metabolism (by serum bone markers) will be undertaken at baseline and at regular intervals during one year of treatment to permit evaluation of the efficacy of these interventions.

BODY:

Overview of Yr3 Progress:

During the third year of this program, the focus has been on completion of recruitment of participants and collection of data. Recruitment was successfully completed in August, 2013, with a total of 50 participants having been enrolled at the Northwestern/RIC site and 11 at the Edward J. Hines, Jr. VA site (see attachment). The Northwestern/RIC site exceeded its target enrollment, both in terms of total numbers (50 vs 40) as well as in speed of enrollment, having reached its original target goal of 40 participants 2 months ahead of schedule. The VA site had a significant delay in being able to begin screening subjects which was a major contributor to their failure to meet the originally projected enrollment goal.

At the end of year 3, there are now 24 participants who have completed the original protocol (23 enrolled at Northwestern/RIC and 1 at the VA; see attachment). Follow-up of study participants has been excellent with only 3 out of 60 (5%) having withdrawn and not available for follow-up. Treatment has been well tolerated and no unexpected safety issues have been identified. The Medical Monitor has reviewed the study at 3 meetings and recommended continuation. Data from all participants who have completed the first year of the study has been entered into the study database and data collection appears to be progressing smoothly at Northwestern/RIC. Serum samples for bone biomarkers from the first 20 participants to have completed the study have been sent for testing to Maine Medical Center Research Institute and CT analyses are up to date.

Because teriparatide treatment continues to be anabolic for more than a single year, we requested to be able to extend treatment for a second year for those participants who wished to do so upon completion of the original protocol. An extension protocol was approved by USAMRMC HRPO and participants are being enrolled and treated with data collection continuing. The existing IND has been updated with this additional information.

Research Accomplishments:

The following items are listed in the statement of work (SOW) for Yr 2 and Yr 3 of the project. Progress and current status are listed for each:

1. Identify and recruit participants: planned enrollment rate is 3 participants/month; 2 participants/month from Northwestern/RIC and 1 participant/month from Edward Hines, Jr VA Hospital.

   Enrollment into the study has been successfully completed. At the Northwestern/RIC site, 23 participants were randomized during the first 10 months of year 3, representing an enrollment rate of 2.3 participants/month, which is above the projected rate of accrual of participants. At the Hines VA site, 10 participants have been enrolled during the past year which is a rate of 0.83 participants/month, only slightly lower than the 1.0 participants/month projected.

2. Perform all study visits, assessments and procedures as outlined in the protocol.

   Study conduct has been excellent. Retention of participants in the study has been better than expected. Only 3 participants who had been entered into the study is no longer being followed (retention rate of 95%).

3. Continuous collect and monitor safety data with reporting as needed to the IRB, Medical Monitor and HRPO.

   All adverse event data are being systematically collected. No unanticipated serious adverse events related to the study interventions (drug or device) have been reported at this time. There have been 3 meetings in Year 3 with the medical monitor and study statistician to review the study procedures and adverse events. An extra meeting with the medical monitor was held to assess the number of fractures during the study. It was concluded that there was no evidence for an increased risk of fractures but this would continue to be monitored. No other potential safety concerns were identified. In all study reviews the recommendation from the medical monitor was to continue the study without changes.

4. Collect, verify and enter all data into the database.

   The research database was finalized and data are being entered. All participants who have completed the trial at Northwestern/RIC have their study data entered. A double-data entry system is being employed to assure high data accuracy.

5. Obtain serum samples and store for batch analysis at the end of the study.

   Serum samples have been collected on all participants and are being stored for batch analysis. Aliquots from the first 20 participants to have finished the study have been sent to Maine Medical Center Research Institute for analysis.

6. Collect all DXA data and enter into database.

All DXA data collected to date have been analyzed and are being entered into the study database.

7. Acquire all CT data and transmit to UIC for analysis.
   CT data acquisition is on-going for all active participants. Data collected to date have been transferred to UIC for analysis. Analysis of these data is currently on-going.

8. Meet every 6 months with Medical Monitor to review safety reports.

   Three meetings with the medical monitor have occurred. An extra visit was planned, as noted above, to review whether the occurrence of fractures represented a safety concern. This was not deemed to be the case. The recommendations from the Medical Monitor have been in all instances to continue the study in its current form. No safety issues have been identified.

9. Complete annual report to IRB and regulatory authorities.

   All annual and regulatory reports have been filed and accepted.

During the past year, the scope of the SOW has been expanded to include continued treatment and follow-up of participants during a second year of study. An extension protocol has been developed, approved by the NU IRB and the USAMRMC ORP HRPO and submitted to the FDA as part of the existing IND. Participants have been offered the opportunity to participate and are doing so, with 8 currently active and others in run-in. In addition, a proposal has been submitted to the DOD Congressionally Directed Joint Warfighters Medical Research Program (JWMRP) to fund the continued extension program.

KEY RESEARCH ACCOMPLISHMENTS:

There are no outcome data available to date. As this is a blinded clinical trial, scientific data relating to study objectives will not be available until all participants have concluded the study, data cleaned and data base locked, and analyses completed.

REPORTABLE OUTCOMES:

The project remains in the phase of data collection. All of the participants have provided baseline data; no data are available of the effects of the interventions being assessed as we remain blinded until completion of data collection.

CONCLUSION:

This project has not progressed to the point of being able to provide any conclusions in regard to the effect of these specific interventions on bone mass or bone quality in people with spinal cord injury. Enrollment has been completed. Data entry is on-going with final data cleaning and data-base lock occurring at the end of year 4. It is anticipated that data analysis will occur during the following year, and a request for extension of the current study without additional funding will be made during year 4.

REFERENCES:

None.

APPENDICES:

None.

SUPPORTING DATA:

Baseline Data of Enrolled Participants

Demographic Data

Mean Age (yr, SD))	41.5 ± 14.4
Sex	22M/6F
Ethnicity	21 Not Hispanic or Latino, 7 Hispanic or Latino
Race	15 Black, 13 White
BMI	24.3 ± 5.0

Clinical Descriptors

Time post-SCI (yr, SD)	16.0±12.1
Injury Level (cervical/thoracic)	8 C/20 Th
Motor Complete/Incomplete	11 Complete/17 Incomplete

Baseline BMD Values (SD)

Spine BMD	0.991 ± 0.15
R Total Hip	0.659 ± 0.11
R Femoral Neck	0.657 ± 0.12
L Total Hip	0.630 ± 0.15
L Femoral Neck	0.637 ± 0.17

Study Status

Enrolled			
	NU	VA	Total
Signed ICF	70	10	80
Screen Failure	40	6	46
Run In	3	3	6
Randomized	27	1	28
Week 2	23	1	24
Week 6	19	1	20
Month 3	18	1	19
Month 6	8	0	8
Month 9	6	0	6
Month 12/Completed	3	0	3
Lost to Follow up	1	0	1